FIVE-MEMBERED 2,3-DIOXO HETEROCYCLES. 21.* REACTION OF 1,5-DIARYL-4-ETHOXYCARBONYL-

TETRAHYDROPYRROLE-2,3-DIONES WITH 2-AMINOPYRIDINE

V. L. Gein, E. V. Shumilovskikh,

É. V. Voronina, and Yu. S. Andreichikov

The reaction of 2-aminopyridine with 1,5-diaryl-4-ethoxycarbonyltetrahydropyrrole-2,3-diones gave 1:1 complexes, which are converted to N-(2-pyridyl)-1,5-diaryl-3-hydroxy-2-oxo-2,5-dihydropyrrole-4-carbox-amides when they are heated above their melting points without a solvent. The character of the hydrogen bonds in the complexes obtained is discussed.

It is known that the reaction of 4-aroyl-1,5-diphenyltetrahydropyrrole-2,3-diones with binucleophiles can be used for the synthesis of condensed systems that contain a pyrrole ring such as pyrrolo[3,4-c]pyrazoles and pyrrolo[3,4-f]diazepines [2].

Nitrogen-containing 2-amino-substituted heterocycles react with β -dicarbonyl compounds to give condensed heterocyclic systems [3]. In this connection it seemed of interest to investigate the reaction of nitrogen-containing 2-amino-substituted heterocycles with 4-aroyl-1,5-diphenyltetrahydropyrrole-2,3-diones, which contain a β -dicarbonyl system. However, the reactivities of the carbonyl groups in the latter are not sufficient for the realization of reactions with 2-amino-substituted heterocycles, and only aliphatic amines can be subjected to reaction with 4-aroyl-1,5-diphenyltetrahydropyrrole-2,3-diones [2]. We have investigated the reaction of 2-aminopyridine with 1,5-diaryl-4-ethoxycarbonyltetrahydropyrrole-2,3-diones Ia-f, which are more reactive with respect to nucleophilic reagents; we established that, regardless of the reaction conditions, the only products of the reaction of tetrahydropyrrole-2,3-diones Ia-f with 2-aminopyridine are 1:1 complexes IIa-f.



1---IIIa R-R¹-H; b R-Br. R¹-H; c R-OMe. R¹-H; d R-H, R¹-NO₂; e R-H, R¹-Me; f R=Br. R¹-Me

Perm Pharmaceutical Institute, Perm 614600. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 32-36, January, 1992. Original article submitted February 12, 1990; revision submitted April 11, 1991.

^{*}See [1] for Communication 20.

- Parisona o	Empirical		IRS	pectrum, cm ⁻	1			PMR spectrum	n,*** ppm		10 P. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1.
nimodilloo	formula	'np,°c¢mi	20	(CO ester)	Ho	NHJ (NHN)	OH NH2 (NII), S	Harom's m	5-11, c	C ₂ H ₅	° 'ntati
lla	C ₂₄ H ₂₃ N ₃ O ₄	183. 185	1610	1660	3140	3295	8,56	7,13	5,81	3,85 q; 1,05 E	69
d11	C ₂₄ H ₂₂ BrN ₅ O ₄	164166	1625	1680	3175	3340		7,24	5,87	3,89 q;1,04 t	85
llc	C25H25N3O5	146148	1620	(1682) 1658	3170	3360		7,11	5,84	3,92 q;1,04 E	86
þri	C24H22N4O6	191193	1625	1675	3175	3360	8,86	7,52	5,98	3,93 q;1,02 t	69
əII	C ₂₅ H ₂₅ N ₃ O ₄	174176	1622	(1672) 1650	3145	3325	7,92	7,06	5,79	3,88 q; 0,98 t	56
Шf	C25H24BrN304	154156	1620	1652	3140	3340	7,92	7.00	5,79	3,919 1,03 t	86
IIIa	C ₂₂ H ₁₇ N ₅ O ₃	252254	i	(1680) 1675	3110	(3350)	(8,31)	7,30	5,98	{	1 9
IIIc	C2311,9N304	227228	B sur	1679	3115	(3360)	(8,08)	7,11	6,04	:	1 9
IIIe	C23H19N3O3	258260	:	1670	3120	(3355)	(8,22)	7,10	5,90		63
Шf	C ₂₃ H ₁₈ BrN ₃ O ₃	234234.5		1680	3110	(3359)	(8,05)	7,22	5,97		96
	•										

TABLE 1. Characteristics of IIa-f and IIIa, c, e, f

*All of the compounds, except IIf, melt with decomposition. **IIc 3.54 ppm (s, CH₃O); IIIc 3.58 ppm (s, CH₃O); IIe 2.07 ppm (s, CH₃); IIf 2.21 ppm (s, CH₃); IIIe 2.15 ppm (s, CH₃); IIIf 2.11 ppm (s, CH₃).

Thus complex IIa is formed by mixing the reactants in dioxane at room temperature, as well as by refluxing in ethanol. Considering the limited solubility of pyrrolediones, the remaining products IIb-f were obtained by refluxing ethanol solutions of the reactants. The resulting complexes are pale-yellow crystalline substances that are soluble in alcohol and dioxane; their structures were confirmed by the spectral data presented in Table 1.

The IR spectra of products IIa-f contain intense absorption bands at 1650-1658 (lactam carbonyl) and 1672-1682 cm⁻¹ (ester carbonyl), as well as broad absorption bands at 3140-3175 (hydroxy group) and 3295-3360 cm⁻¹ (NH₂ group). In addition to multiplets of protons of aromatic rings and groups bonded to them, the PMR spectra of complexes IIa-f contain a triplet and quartet of protons of an ethoxy group at 0.98-1.05 and 3.85-3.93 pp, respectively, a singlet of a methylidyne proton in the 5 position of the heteroring at 5.81-5.98 ppm, and a broad signal corresponding to three protons of OH and NH₂ groups at 7.92-8.86 ppm.

The mass spectrum of complex IIe contains a molecular-ion peak with m/z 337, as well as peaks of fragment ions with m/z 291 $[M - C_2H_5OH]^+$, 263 $[M - C_2H_5OH - CO]^+$, 246 $[M - CH_3C_6H_4]^+$, 235 $[M - C_2H_5OH - 2CO]^+$, 204 $[M - CH_3C_6H_4N=C=O]^+$, 194 $[C_6H_5C=NC_6H_4CH_3]^+$, 174 $[C_6H_5C=CCOOC_2H_5]^+$, 146 $[C_6H_5CH=CHCOO]^+$, and 134 $[CH_3C_6H_4NH-C=O]^+$; this corresponds to fragmentation of the starting 1-(p-tolyl)-5-phenyl-4-ethoxycarbonyl-tetrahydro-pyrrole-2,3-dione. The fragment peak with m/z 93 $[\alpha$ -NH-Py]⁺ indicates the presence of 2-aminopyridine in the complex. All of the IIa-f obtained give an intense cherry-red coloration with an alcohol solution of FeCl₃; this constitutes evidence for retention of the enol hydroxy group in them. ,The formation of the complexes evidently takes place through donor-acceptor interactions between 2-aminopyridine and the tetrahydropyrrole-2,3-diones.

The participation of the ester and lactam carbonyl groups in complexing is confirmed by the 30-40 cm⁻¹ decrease in the IR spectra of the corresponding bands of the stretching vibrations of complexes IIa-f as compared with the bands of the starting 1,5-diaryl-4-ethoxycarbonyltetrahydropyrrole-2,3-diones. When we recorded the IR spectra of complex IIa in solution in chloroform, we observed that at a solution concentration of $2.8 \cdot 10^{-2}$ mole/liter the absorption bands of the lactam and ester carbonyl groups are shifted 30-45 cm⁻¹ (to 1715 cm⁻¹) to the high-frequency region. The absorption bands of the N—H and O—H bonds are also shifted to the high-frequency region and are observed at 3350, 3410, and 3500 cm⁻¹. Further dilution of the solution to a concentration of $3.5 \cdot 10^{-3}$ mole/liter has virtually no effect on the IR spectrum of complex IIa. Similar changes in the IR spectra on passing from suspensions in mineral oil to dilute solutions in chloroform are also observed for IIb-f. All of this provides evidence that polymeric complexes in which the 2-aminopyridine and tetrahydropyrrole-2,3-dione molecules are linked by intermolecular hydrogen bonds due to interaction of the ester or lactam carbonyl groups with the hydrogen atoms of the NH₂ group of 2-aminopyridine, as well as interaction of the hydrogen atoms of the enol hydroxy group with the nitrogen atom of the pyridine ring, are evidently formed in the crystalline state.



Upon sufficient dilution the complexes are destroyed, and this leads to a shift of the absorption bands in the IR spectra to the higher-frequency region.

When complexes IIa-f are heated in the absence of a solvent at 165-200°C for 10-40 min, they decompose to give N-(2-pyridyl)-1,5-diaryl-3-hydroxy-2-oxo-2,5-dihydropyrrole-4-carboxamides IIIa, c, e, f (see Table 1).

The IR spectra of IIIa, c, e, f contain absorption bands of NH and OH groups at 3350-3360 and 3110-3120 cm⁻¹, and an intense band at 1670-1680 cm⁻¹, which is due to stretching vibrations of lactone and amide carbonyl groups, is observed. The signals of the protons of an ethoxy group that are present in the spectra of the complexes of tetrahydropyrrole-2,3-diones vanish in the PMR spectra of IIIa, c, e, f. A singlet of a methylidyne proton at 5.97-6.04 ppm, a multiplet of aromatic protons centered at 7.10-7.30 ppm, and a singlet of the proton of an amide group at 8.05-8.31 ppm are observed in them. The signal of the proton of the enol hydroxy group evidently coincides with the signals of the aromatic protons.

The mass spectrum of IIIa contains a molecular-ion peak with m/z 371, peaks of fragment ions with m/z 277 $[M - C_5H_5NNH_2]^+$ and 251 $[M - C_5H_5NNHCO]^+$, and peaks with m/z 149 $[PhNCOCOH]^+$ and 94 $[C_5H_5NNH_2]^+$.

Judging from the literature data, 1,5-diaryl-4-ethoxycarbonyltetrahydropyrrole-2,3-diones do not form amides on reaction with aromatic amines but are converted exclusively to 3-arylamino-4-ethoxycarbonyl-1,5-diaryl-2,5-dihydro-2-pyrrolones [4].

The formation of 2-pyridylamides IIIa, c, e, f that we observed is evidently explained by drawing together of the amino and ester groups in a complex, which substantially decreases the energy of activation of nucleophilic substitution of the ethoxy group. To prove the presence of an enol hydroxy group in the indicated amides we studied the reaction of IIIa with diphenyldiazomethane; N-(2-pyridyl)-1,5-diphenyl-3-diphenylmethoxy-2-oxo-2,5-dihydropyrrole-4-carboxamide (IV) was isolated as the only product.

In contrast to the analogous 4-ethoxycarbonyltetrahydropyrrole-2,3-dione derivatives [5], the product obtained did not undergo 1,3-signatropic migration of a diphenylmethyl group on heating to 200°C.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer. The PMR spectra were obtained with an RYa-231 spectrometer (60 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The mass spectrum was obtained with an MKh-1320 spectrometer with an ionizing-radiation energy of 70 eV.

The results of elementary analysis of IIa-f, IIIa, c, e, f, and IV for N and Br were in agreement with the calculated values.

Complexes (Ha-f) of 1,5-Diaryl-4-ethoxycarbonyltetrahydropyrrole-2,3-diones with 2-Aminopyridine. 2-Aminopyridine (10 mmole) was added to a solution of 10 mmole of one of the tetrahydropyrrole-2,3-diones Ia-f in 50 ml of ethanol, and the reaction mixture was refluxed for 3 h and then cooled. The resulting precipitate was removed by filtration and recrystallized from toluene or acetonitrile. This procedure was used to obtain the corresponding complexes IIa-f.

Complex IIa-f was also obtained by adding a solution of 0.47 g (5 mmole) of 2-aminopyridine in 5 ml of dioxane to a solution of 1.62 g (5 mmole) of 1,5-diphenyl-4-ethoxycarbonyltetrahydropyrrole-2,3-dione in 20 ml of dioxane while maintaining the reaction mixture at 20°C for 1 h and recrystallizing the isolated product from toluene.

N-(2-Pyridyl)-1,5-diaryl-3-hydroxy-2-oxo-2,5-dihydropyrrole-4-carboxamides (IIIa, c, e, f). A 2.24-mmole sample of one of the complexes IIa, c, e, f was maintained at a temperature 10-20°C above its melting point, i.e., at 165-200°C, for 10-40 min, after which the reaction mixture was treated with ethanol, and the precipitate was removed by filtration and recrystallized from dioxane or DMSO. This procedure was used to obtain the corresponding products IIIa, c, e, f.

N-(2-Pyridyl)-1,5-diphenyl-3-diphenylmethoxy-2-oxo-2,5-dihydropyrrole-4-carboxamide (IV, $C_{35}H_{27}N_3O_3$). A solution of 0.21 g (1 mmole) of diphenyldiazomethane in 5 ml of dioxane was added to a solution of 0.37 g (1 mmole) of IIIa in 10 ml of dioxane, after which the reaction mixture was stirred with heating to 80°C for 2 h until the color changed from crimson to yellow. The solvent was then evaporated, and the residue was recrystallized from toluene to give 0.39 g (72%) of IV with mp 180-181°C. IR spectrum (thin layer): 3350 (N–H), 1689 (lactam C=O), 1670 cm⁻¹ (amide C=O). PMR spectrum (d₆-DMSO): 6.26 (1H, s, 5-H), 7.45 (24H, m, C₆H₅), 9.95 ppm (1H, s, NH).

LITERATURE CITED

- 1. V. L. Gein, O. I. Ivanenko, A. N. Maslivets, and Yu. S. Andreichikov, Zh. Org. Khim., 26 (1990, in press).
- 2. Yu. S. Andreichikov, V. L. Gein, and I. N. Anikina, Zh. Org. Khim., 22, 1749 (1986).
- 3. H. Reimlinger, F. Billiau, M. Peiren, and R. Merenyi, Chem. Ber., 105, 108 (1972).
- 4. I. R. Merchant and V. Srinivasan, Rec. Trav. Chem., 81, 144 (1962).
- 5. Yu. S. Andreichikov, V. L. Gein, and E. V. Shumilovskikh, Khim. Geterotsikl. Soedin., No. 6, 753 (1990).